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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,777	07/13/2001	James Chen	600057.446C1	5768

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/905,777	CHEN, JAMES	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-21 and 25-28* is/are pending in the application.

4a) Of the above claim(s) *13,14 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-12, 15-21, 25, 27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim 2 has been amended. Claims 1-21 and 25-28 are pending. Claims 13, 14 and 26, drawn to non-elected species remain withdrawn from consideration. Claims 1-12, 15-21, 25, 27 and 28 are under consideration to the extent that they read on (d) tumor surface antigen, (e)tumor endothelial antigen, and (g) tumor vessel wall antigen.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 2, 3, 9-12, 15-21, 25, 27 and 28 under 35 U.S.C. 103(a) as being unpatentable over Abels et al (WO 97/31582) in view of the abstract of Goetz et al (WO 97/33620), Schultes et al (SPIE, 1994, Vol. 148, pp. 148-157) and Theodore et al (WO 95/15979) is maintained for reasons of record.

Abels et al teach a photodynamic method for treating highly vascularized tumors and their metastases, such as Kaposi's sarcoma; adenocarcinoma of the colon, esophagus, breast; neurofibroma and malignant melanoma (page 8, line 22 to page 9, line 11) comprising administering indocyanine green (ICG), followed by irradiation with light, either continuous or pulsed, at a substantially lower intensity than used with photothermal therapy (page 10, lines 11-14 and lines 18-20) which fulfills the specific limitation of claim 18. Abels et al teach a light source which is a laser diode (page 15, lines 1-3) which fulfills the specific limitation of claim 3. Abels et al teach fluence rates of less than 10W/cm2, including 5mW/cm2 to 5W/cm2, 10mW/cm2 to 3W/cm2, 25mW/cm2 to 2W/cm2 and 40mW/cm2 to 500mW/cm2, and for deeper tumors, 2W/cm2 to 5W/cm2 (page 8, lines 14-21). Abels et al teach that a typical total light dose is 100j/cm2 but that the dose can vary from 10J/cm2 to 200J/cm2 (page 14, lines 18-20) and that a diode laser can be used anywhere in the range of 770-840nm, but preferably at 805nm or 800nm because 800nm is the wavelength at which absorption of light by body pigments and

blood is negligible allowing light penetration to greater depths (page 15, lines 1-10). It is noted that 805nm is the absorption maximum of ICG (page 3, lines 4-6) and thus irradiation at 805nm fulfills the limitation of claim 12, requiring a single photon absorption mode. Abel et al rely on the natural accumulation of ICG within the microcirculation of oncological lesions (page 3, lines 11-22). Abels et al teach the administration of ICG in a liposomal preparation (page 9, line 17 to page 9, line 2). Abel et al do not teach the first and second conjugates of claim 2.

Schultes et al teach that administration of an antibody conjugated photosensitizer versus the photosensitizer alone, allows for a reduction in the dose of photosensitizer used and the more selective binding to target cells allows for reduced cutaneous photo toxicity (page 156, lines 24-31).

The abstract of Goetz et al teaches an IGC antibody conjugate for the treatment of tumors.

Theodore et al teach a method of increasing photosensitizing active agent localization at a target cell site within a mammalian recipient, which method comprises: administering to the recipient a first conjugate comprising a targeting moiety and a member of a ligand-anti-ligand binding pair, wherein the first conjugate localizes at a target site; and administering to the recipient a second conjugate comprising a photosensitizing agent and a ligand/anti-ligand binding pair member, wherein the second conjugate binding pair member is complementary to that of the first conjugate, and wherein the photosensitizing agent or the second conjugate is chemically modified to induce rapid renal clearance thereof from the recipient. Theodore et al teach that the photosensitizing agent absorbs light at wavelengths ranging from about 600 to about 800 nm, and the photosensitizing agent is selected from the group consisting of porphyrin derivatives with a strong absorption band between 600 and 700 nm; phthalocyanines chelated with aluminum or zinc; an ether/ester derivative of porphyrin; chlorins; purpurins; and benzoporphyrin derivatives (claims 17-20). Theodore et al teach the delivery of photosensitizing agent to target cells through the pre-targeting approach using ligand or antigen derivatized liposomes (page 102, lines 24-30 and page 113, line 29 to page 114, line 11).

It would have been prima facie obvious at the time the claimed invention was made to use a pre-targeting system for the administration of ICG in a method to kill the highly vascularized tumor cells as taught by Abels et al, and to use liposomes loaded with said

photosensitizer wherein said liposomes are attached to a ligand of the pre-targeting system. One of skill in the art would have been motivated to do so by the teachings of Theodore et al on the improvements in targeting tumor cells by using pre-targeting system rather than direct targeting, the further specific teaching of Theodore et al on the targeting of antigen-derivatized liposomes which could be used in the pre-targeting system and the suggestion by Abels et al that ICG be administered in a liposomal preparation.

Applicant argues that Abels teaches away from the instant invention because Ables teaches lesions which are not in the vascular system, such as melanomas or adenocarcinomas. this has been considered but not found persuasive. Abels teaches a photodynamic method for treating highly vascularized tumors and their metastases, such as Kaposi's sarcoma; adenocarcinoma of the colon, esophagus, breast; neurofibroma and malignant melanoma (page 8, line 22 to page 9, line 11). Because the tumors are highly vascularized, they are without a doubt within the vascular system. Applicant argues that the photosensitizing agent is cleared from the skin and subcutaneous tissues and that upon reading of Ables, one of skill in the art would conclude that the method would not be appropriate for the treatment of vascular lesions. This has been considered but not found persuasive. Abels teaches the clearing of the photosensitizing agent from non-target tissues which are not highly vascularized. Applicant argues that Schultes fails to overcome the deficiencies of Ables because Schultz fails to teach targeting lesions of the vascular system this has been considered but not found persuasive. Schultz need not teach the targeting of the vascular system, because that point was taught by Abeles. Schultz is relied upon for teaching that conjugated photosensitizer is preferred over the photosensitizer alone. Applicant also argues against the Goetz , and Theodore, similarly stating that they do not teach the targeting of lesions in the vascular system. This is not persuasive because Ables teaches the targeting of lesion in the vascular system and therefore there is no deficiency in the combination of references.

The rejection of claims 1-12, 18-21, 25 and 28 under 35 U.S.C. 103(a) as being unpatentable over Abels et al (WO 97/31582) and Schultes et al (SPIE, 1994, Vol. 148, pp. 148-157) in view of Williams (U. 5,576,013, reference "AJ" of the IDS submitted October 8, 2003),

Ruoslahti et al (U.S. 6,180,084) and Chen (U.S. 5,445,608, reference "D" of the IDS submitted April 4, 2002) is maintained for reasons of record.

Claim 4 embodies the method of claim 1 wherein said light is directed through the skin in a direction parallel and lengthwise to the wall of the vascular vessel having the lesion. Claim 5 embodies the method of claim 3 wherein said laser diode is a light emitting strip and wherein said light emitting strip is placed over the skin overlying the lesion. Claim 7 embodies the method of claim 5 wherein said optical fiber diffuses said light when placed over the vessel wall having the lesion. Claim 8 embodies the method of claim 5 wherein said light source is a mar comprising a plurality of said optical fiber.

Abels et al teach a photodynamic method for treating highly vascularized tumors and their metastases, such as Kaposi's sarcoma; adenocarcinoma of the colon, esophagus, breast; neurofibroma and malignant melanoma (page 8, line 22 to page 9, line 11) comprising administering indocyanine green (ICG), followed by irradiation with light, either continuous or pulsed, at a substantially lower intensity than used with photothermal therapy (page 10, lines 11-14 and lines 18-20) which fulfills the specific limitation of claim 18. Abels et al teach a light source which is a laser diode (page 15, lines 1-3) which fulfills the specific limitation of claim 3. Abels et al teach fluence rates of less than 10W/cm2, including 5mW/cm2 to 5W/cm2, 10mW/cm2 to 3W/cm2, 25mW/cm2 to 2W/cm2 and 40mW/cm2 to 500mW/cm2, and for deeper tumors, 2W/cm2 to 5W/cm2 (page 8, lines 14-21). Abels et al teach that a typical total light dose is 100j/cm2 but that the dose can vary from 10J/cm2 to 200J/cm2 (page 14, lines 18-20) and that a diode laser can be used anywhere in the range of 770-840nm, but preferably at 805nm or 800nm because 800nm is the wavelength at which absorption of light by body pigments and blood is negligible allowing light penetration to greater depths (page 15, lines 1-10). It is noted that 805nm is the absorption maximum of ICG (page 3, lines 4-6) and thus irradiation at 805nm fulfills the limitation of claim 12, requiring a single photon absorption mode. Abel et al rely on the natural accumulation of ICG within the microcirculation of oncological lesions (page 3, lines 11-22). Abel et al do not teach the conjugation of ICG to a ligand which targets the tumor neovasculature.

Schultes et al teach that administration of the antibody conjugated photosensitizer versus the photosensitizer alone, allows for a reduction in the dose of photosensitizer used and the more

selective binding to target cells allows for reduced cutaneous photo toxicity (page 156, lines 24-31).

Ruoslahti et al teach the targeting of cytotoxic agents to angiogenic vasculature of a tumor by means of peptides which bind to the NGR receptor in the tumor neovasculature (column 2, lines 63-67 and column 66, lines 20-23).

Williams et al teach locally applying a photosensitizing agent such as indocyanine green (column 5, line 11) to target tissue consisting essentially of blood carrying vessels supplying an undesired lesion such as a neoplastic or neovascular lesion (column 3, lines 46-52 and claims 1 and 7) which is consistent with the targeted localization of photosensitizing agents by means of specific ligands which bind to the tumor vasculature. Williams et al teach that targeting the blood supply of a lesion is more effective than targeting the lesion itself (column 3, lines 46-59) and therefore requires less energy (column 5, lines 19-21). Williams et al teach that indocyanine green is effective to coagulate blood in the vessels of the target tissues (column 5, lines 6-8 and 11).

Chen disclose an apparatus for photodynamic therapy comprising a probe having one or a plurality of laser diodes, light emitting diodes, electroluminescent light source; incandescent light sources; cold cathode fluorescent light sources; organic polymer light sources; or inorganic light sources, wherein the light source is adapted for implantation in a treatment area within a patient, wherein said probe is flexible allowing for transplantation within a treatment site in a patient. Chen discloses probes comprising optical fiber bundles (Figures 14 and 15) which are flexible, an optical fiber diffuser (claim 34 c), and a plurality of LEDs (Figure 11) which are suitable to apply PDT to external surfaces of the body (column 24, lines 37-41).

It would have been prima facie obvious at the time the claimed invention was made to administer ICG conjugated to the peptides of Ruoslahti et al for the selective localization of said ICG to the tumor vasculature and use the probes disclosed by Chen for applying light to a vessel supplying a tumor, either by external application of the light, or by internal application of light via the using the probes of Chen as implants in a method wherein ICG was targeted to the tumor neovasculature by conjugation with molecules which bind . One of skill in the art would have been motivated to do so by the teachings of Williams et al on the efficacy of targeting the blood supply of the tumor lesion rather than the lesion itself. One of skill in the art would have been

motivated to use a conjugate of the ICG to the tumor homing peptides in order to concentrate the ICG in the affected area and reduce the dose of ICG and undesirable Cutaneous effects associated with the higher dose of ICG as taught by Schultes. One of skill in the art would have been specifically motivated to use the peptides as taught by Ruoslahti et al in order to localize the ICG in the tumor vasculature making it available to damage the blood supply of the tumor as taught by Williams et al to be more effective and require less energy than the targeting of the tumor itself.

Applicant maintains argument against the Abeles as stated above and states that Ruoslahti et al teaches only tumor targeting molecules, and Chen only teaches the apparatus for delivering light activated therapy and therefore fails to remedy the deficiencies of Ables et al. However, as stated above, Ables et al is not deficient in teaching targeting highly vascularized tumors and therefore tumors in the vascular system and thus needs none of the combined references to further teach this point.

Applicant admits that the method of Williams would have the effect of creating a blood clot in the vascular system. This has been considered but not found persuasive. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case Williams teaches the notion of targeting the blood supply of the tumor lesion rather than the lesion itself.

The primary point of contention between applicant and the examiner seems to be what constitutes a lesion in the vascular system in light of the elected species of tumor surface antigen, tumor endothelial antigen, and tumor vessel wall antigen. It is well known in the art that tumors can direct the formation of local vascularity by the process of angiogenesis which can supply the growing tumor with blood from the vascular system. As such the vascularized tumors are part of the vascular system because they are a vascular system.

All claims are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/

Ph.D., Primary Examiner

Art Unit 1643